

Primary Prevention of Congenital Anomalies: Recommendable, Feasible and Achievable

Domenica Taruscio^a Alberto Mantovani^b Pietro Carbone^a Ingeborg Barisic^e
Fabrizio Bianchi^c Ester Garne^f Vera Nelen^g Amanda Julie Neville^d
Diana Wellesley^h Helen Dolkⁱ

^aNational Center for Rare Diseases, and ^bDepartment of Food Safety and Veterinary Public Health, Istituto Superiore di Sanità, Rome, ^cUnit of Epidemiology, IFC CNR (Tuscany Registry of Birth Defects), Pisa, and ^dIMER Registry (Emilia Romagna Registry of Birth Defects), Ferrara, Italy; ^eChildren's University Hospital of Zagreb, Clinical Hospital Center Sisters of Mercy, Zagreb, Croatia; ^fHospital Lillebælt, Kolding, Denmark; ^gProvincial Institute for Hygiene, Antwerp, Belgium; ^hFaculty of Medicine, University Hospitals Southampton and Wessex Clinical Genetics Service, Southampton, and ⁱWHO Collaborating Centre for the Surveillance of Congenital Anomalies, University of Ulster, Ulster, UK

Key Words

Congenital anomalies · EUROCAT · EUROPLAN · Health policies · Periconceptional service · Preconception care · Preconception counseling · Prevention of congenital abnormalities · Primary prevention · Public health · Rare diseases

Abstract

Primary prevention of congenital anomalies was identified as an important action in the field of rare diseases by the European Commission in 2008, but it was not included in the Council Recommendation on an action in the field of rare diseases in 2009. However, primary prevention of congenital anomalies is feasible because scientific evidence points to several risk factors (e.g., obesity, infectious and toxic agents) and protective factors (e.g., folic acid supplementation and glycemic control in diabetic women). Evidence-based community actions targeting fertile women can be envisaged, such as risk-benefit evaluation protocols on therapies for

chronic diseases, vaccination policies, regulations on workplace and environmental exposures as well as the empowerment of women in their lifestyle choices. A primary prevention plan can identify priority targets, exploit and integrate ongoing actions and optimize the use of resources, thus reducing the health burden for the new generation. The EUROCAT-EUROPLAN recommendations for the primary prevention of congenital anomalies endorsed in 2013 by the European Union Committee of Experts on Rare Diseases present an array of feasible and evidence-based measures from which national plans can adopt and implement actions based on country priorities. Primary prevention of congenital anomalies can be achieved here and now and should be an integral part of national plans on rare diseases.

© 2015 S. Karger AG, Basel

Congenital anomalies (CA) are an important cause of infant and childhood death, chronic illness and disability worldwide. World Health Organization data show that

CA are a global health issue affecting around 1 in 33 infants and producing an estimated burden of approximately 3.2 million cases of disability and 270,000 deaths during the first 28 days of life every year. In addition, CA-induced long-term disabilities may have a significant impact on individuals, families, health care systems and society [1]. The risk factors associated with CA often increase the risk of other adverse birth outcomes, such as preterm birth and low birth weight and neurodevelopmental outcomes, also increasing the short- and long-term health burden for the new generation [2].

Several environmental and exogenous factors and agents are strongly suspected or proven to damage or cause the abnormal development of the fetus [3]. As most CA are multifactorial, there is an interaction between risk factors and genetics. CA occur more frequently among resource-constrained families and in countries where mothers may have increased and concurrent exposure to a number of relevant factors, such as imbalanced nutrition, poor environment and lifestyle as well as infections [4].

Scientific evidence shows that by reducing recognized risk factors (or enhancing protective factors) it is possible to lower the incidence of CA. Two European projects, EUROCAT (European Surveillance of CA; <http://www.eurocat-network.eu/>) and EUROPLAN (European Project for Rare Diseases National Plans Development; <http://www.europlanproject.eu/>), have recently issued a body of evidence-based recommendations for CA primary prevention, which was endorsed by the European Union Committee of Experts on Rare Diseases in 2013 [5]. These recommendations allow primary prevention strategies to be developed both for specific target groups (e.g., counselling of fertile women with chronic illness on the risks and benefits of medication choices) and broader public health targets relevant to prenatal development (e.g., community policies promoting healthier dietary patterns or reducing active/passive smoking). Each recommendation implemented can favorably impact a CA or a group of CA: an improved folate status can reduce the risk of neural tube defects [6], whilst the avoidance of tobacco smoke and alcohol intake can reduce the risk of orofacial clefts and congenital heart disease [7, 8] and fetal alcohol syndrome [9], respectively. However, concerted group actions aimed at protecting the conceptus may likely achieve an added value higher than the sum of individual, isolated and uncoordinated, albeit valuable, measures. It should be recognized that public health actions, and especially primary prevention, currently have to face resource restrictions by policy makers; however, an evi-

dence-based primary prevention plan on CA would rely on the integration of actions that are already in place in most industrialized countries and in several industrializing countries, and, thus, a primary prevention plan would be cost-effective and may indeed spare resources, i.e., by optimizing their use. In developing countries with less primary prevention in place, a first phase of recognition may indicate the priority targets on which to devote the limited resources available. Although EUROCAT has been awarded funding from 2011 to become a joint action between the EU and the member states [10], national governments or other bodies responsible for funding have usually contributed precariously and with short-term funding contracts to support the national, regional or local CA registries [11].

The availability of CA registries is important to estimate the health burden of CA, identifying possible hot spots and assessing the impact of interventions [12]. Extending such tools globally on the basis of up-to-date quality standards is paramount for robust and sustainable primary prevention plans. Policies to minimize the exposures to teratogenic chemicals may impact on the trade of products and/or foods, and, thus, such policies would be better implemented at a transnational level. The European Union has built two important systems based on the risk assessment of foods and chemicals that pivot on the European Food Safety Authority (EFSA; <http://www.efsa.europa.eu>) and the European Chemical Agency (ECHA; <http://www.echa.europa.eu/>). In the global internet era, communities and individuals often actively seek information and wish to know about important issues such as the health of their children. Indeed, this situation should be seen as a potential resource, as the empowerment of women can be a critical driving force for primary prevention policies. How to achieve such empowerment is definitely a challenge for current multicultural societies.

EU Member States are implementing national plans (or strategies) on rare diseases (RD) [13, 14], and most CA meet the criteria for being considered as an RD [15]. Indeed, CA represent an important fraction of RD and, due to the critical role of nongenetic factors in their pathogenesis, are the RD group in which primary prevention measures may have a beneficial impact. Primary prevention of CA was identified as an important action in the field of RD in the Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions of November 11, 2008 [16]; however, it has not been included in the Council Recommendation on an action in the field of RD of June 8, 2009 [13].

In the past century, significant progress has been made in identifying many modifiable risk or preventive factors for birth defects [17]. Available scientific evidence indicates that acting on identified risk and protective factors can achieve a reduction in CA incidence and the related health and social burden [5]. Unfortunately, for most factors identified, a translation of scientific and epidemiologic findings into successful strategies for birth defect prevention in the population has not occurred [16–18]. Moreover, it is often insufficiently recognized that between the scientific evidence concerning a risk factor and a successful public health action, another layer of scientific evidence is needed from public health research that concerns the evidence base for complex interventions and behavior change strategies. Therefore, primary prevention of CA should be an integral part of national plans on RD.

Instruments, in particular CA registries, should be implemented or put in place to monitor the actual implementation of planned actions and their efficacy. As advances in knowledge lead to changes and the development of evidence, mechanisms should be envisaged for the consistent and timely translation of scientific knowledge into evidence-based actions as well as for identifying relevant knowledge gaps. Otherwise, the effectiveness of primary prevention efforts may not be fully realized. For this purpose, it will be very useful to maximize the public health surveillance and related research mechanisms to monitor public preconception health. Community health data are already used systematically in several European states to conduct public health surveillance to evaluate and improve health, health programs and health policy [19]. Several public health agencies in Europe conduct surveillance and maintain data collection and surveillance systems in the field of maternal and child health benefits. It is important to apply public health surveillance strategies to monitor selected preconception health indicators (e.g., folic acid supplementation, smoking cessation, alcohol misuse, drug use, obesity and vaccinations) and to develop or modify existing measures to monitor evidence-based interventions used in preconception health services [20].

Issues related to multifactorial endocrine-related disorders, food and nutrition provide an example of knowledge requirements and gaps for updating primary prevention policies.

Rather than focusing on teratogenic risk only, many recent papers deal with risk-benefit analyses of interventions for chronic health conditions that can affect a significant fraction of fertile women (table 1). Conditions

such as thyroid diseases [21, 22] or type 2 diabetes (T2D) [23–26] may themselves pose a risk to the conceptus. The challenge is therefore to design treatments that are effective and do not pose an additional, or different, risk to the conceptus as compared to the disease itself. For instance, as hyperthyroidism has been reported in 3% of pregnant women [27], a balanced therapy has been proposed with propylthiouracil (less damaging to the embryo but inducing long-term liver toxicity) in the first trimester, followed by the use of methimazole (which has a higher teratogenic potential but lower maternal toxicity) [21]. However, for chronic conditions, the primary prevention of CA and other adverse pregnancy outcomes has to integrate patient-oriented periconceptional actions with actions at the community level involving food, lifestyle and health care.

An adequate dietary intake of iodine (through seafood, dairy and eggs), possibly supported by the use of iodized salt, is a basic requirement for proper thyroid function, which is critical for intrauterine growth and development. A high intake of goitrogens (e.g., isoflavones, thiocyanates and nitrates from vegetables) or subclinical deficiencies of some nutrients (e.g., selenium) may aggravate the effect of low iodine, especially when there are additional needs as in pregnancy [28]. In particular, the intake of selenium has been thought to prevent autoimmune hypothyroidism, an important disease in fertile women, but this hypothesis is not supported by robust evidence [29].

Pregnant women with either type 1 diabetes or with T2D essentially show the same risk of CA because maternal hyperglycemia is the key teratogenic factor [30]. However, T2D represents the highest public health concern; its incidence is rising globally, calling for primary prevention strategies based on awareness raising and lifestyle modifications also in emerging economies [31]. Notwithstanding its complex pathogenesis and undisputed genetic predisposition, the risk of T2D may be reduced by the diffusion of healthier nutritional choices and increased physical activity, adjusted to reflect local food availability and the individual's needs [32]. Basic primary prevention is paramount to build up the health of the community as well as of the next generations, and, thus, it should start with education and empowerment from early childhood. Against this background, preconceptional care of the many women currently affected by T2D will increase their potential for healthy motherhood. The available guidelines pivot on the preconception control of blood glucose and metabolism as a priority action [23, 25]. Other recommendations, though not completely consistent,

Table 1. Description of systematic reviews regarding interventions or recommendations used for women with thyroid disorders and diabetes before and/or during pregnancy

Study	General topics of the review	Objectives of the review	Type of studies or documents reviewed	Number of studies included in the review	Conclusions
Earl et al. [21], 2013	Women before or during pregnancy with hyperthyroidism	To identify interventions used in the management of hyperthyroidism before or during pregnancy and to ascertain the impact of these interventions on important maternal, fetal, neonatal and childhood outcomes	Randomized controlled trials, quasi-randomized controlled trials and cluster-randomized trials	No trials were included in the review	No evidence found from randomized trials to help inform women and their doctors about which antithyroid drugs are most effective, with the lowest potential for harm
Reid et al. [22], 2013	Pregnant women with a diagnosis (either before or during pregnancy) of hypothyroidism, subclinical hypothyroidism or isolated maternal hypothyroxinemia	To identify interventions used in the management of hypothyroidism and subclinical hypothyroidism before or during pregnancy and to ascertain the impact of these interventions on important maternal, fetal, neonatal and childhood outcomes	Randomized controlled trials and quasi-randomized controlled trials are included	Four randomized studies (involving 362 women) were included in the review	There are currently insufficient data in this review to support any recommendations for practice for the treatment of clinical and subclinical hypothyroidism before and during pregnancy
Mahmud and Mazza [23], 2010	National and international guidelines that are concerned with the preconception care of women with diabetes	To compare and contrast the quality and content of guideline recommendations for the preconception care of diabetic women	National and international English language guidelines published from 2001 to May 2009	Five guidelines were included in the review	International guidelines for the care of women with diabetes who are contemplating pregnancy are consistent in their recommendations
Wahabi et al. [24], 2012	Women of reproductive age with type 1 or type 2 pregestational diabetes mellitus who were not pregnant at the time of intervention	To assess the effectiveness and safety of prepregnancy care in improving the congenital malformation and perinatal mortality	Randomized trials (including cluster and quasi-randomized trials) and cohort and case control studies are included	A total of 25 reports of 21 studies were included in the review	Prepregnancy care reduced the rate of congenital malformation from 7.4 to 1.9%
Tieu et al. [25], 2010	Women of reproductive age with pre-existing diabetes mellitus (type 1 or type 2) who are not currently pregnant	To assess the effects of preconception care in women with preexisting diabetes on health outcomes for mother and baby	Randomized controlled trials, quasi-randomized controlled trials and cluster-randomized trials are included	One trial (involving 53 women) was included in the review	Little evidence is available to recommend for or against preconception care for women with preexisting diabetes
Tieu et al. [26], 2013	Women who have been diagnosed with gestational diabetes mellitus in a previous pregnancy: type 1 or type 2 diabetes	To investigate the effects of interconception care for women with a history of gestational diabetes mellitus on maternal and infant health outcomes	Randomized controlled trials, quasi-randomized controlled trials and cluster-randomized controlled trials are included	No completed studies that met the inclusion criteria of the review were found; one ongoing clinical trial was identified	The role of interconception care for women with a history of gestational diabetes mellitus on maternal and infant health outcomes remains unclear

recommend high-dose folate supplementation (5 mg/day) as well as empowering the woman by encouraging regular exercise, weight management and a diet with high levels of complex carbohydrates, soluble fiber and vitamins and reduced levels of saturated fats [23]. Striving to reduce blood glucose might increase the risk of serious maternal hypoglycemia in the first trimester [24]; thus, rather than ‘fighting diabetes’, the preconceptional strat-

egy should aim at supporting the woman to maintain her health. Noticeably, insufficient data exist on how interconception care may protect maternal and infant health in women with a history of gestational diabetes [26]. Another related metabolic condition, obesity, shares many features with T2D. The global rise in obesity involves low- and middle-income countries [31, 33]. Obesity has a complex pathogenesis involving lifestyle (high-density

caloric diets, low physical activity), genetic predisposition and probably also developmental exposures to endocrine disrupters [34]. Maternal obesity increases the risk of pregnancy complications and CA, including neural tube defects [35]. Therefore, primary prevention of obesity-related birth outcomes should integrate community actions, including a safer environment, and targeted preconceptional care for women that are obese, both levels emphasizing the empowerment to healthier diets and reasonable physical activity [26]. The primary prevention of T2D and obesity share many features and should be integrated in a concerted and cost-effective public health plan for the population as a whole, but with special reference to pregnancy [31].

The CA risk associated with endocrine-metabolic disorders also point out the central role of nutrition. A recent US study pointed out that rather than taking supplements, a prudent overall dietary pattern may reduce the risk of neural tube and congenital heart defects [36]. It is well established that within an adequate diet, a well-balanced intake of specific nutrients (e.g., zinc and vitamin A) is critical for the prevention of CA; also, whereas a folate-rich diet and periconceptional supplementation with folic acid are effective beyond doubt in reducing the prevalence of neural tube defects, attention should also be given to the status of vitamins B₁₂ and B₆, since they are needed for proper folate metabolism [5]. Considering the global problem of an inadequate or unbalanced intake of micronutrients, it is plausible that multiple micronutrient supplementation would represent a major tool in the prevention of CA. Moreover, the composition of multiple supplements should be carefully worked out, considering the too often overlooked toxicity of nutrients: high doses may be harmful or, as in the case of many trace elements, may impair the bioavailability of other nutrients [37]. Additional scientific evidence could also refine and improve the undisputed effectiveness of folic acid supplementation. Issues for research include the characterization of effects on CA other than neural tube defects [38, 39], the 5-methyl-tetrahydrofolate as possible alternative to folic acid [40] and the mechanisms (immune factors, inositol metabolism) and risk factors of the neural tube defects that are resistant to folic acid supplementation [41, 42]. Most importantly, folic acid is also an issue for public health research, e.g., strategies to promote a community awareness on periconceptional supplementation [43] and a robust and consistent definition of recommended intake levels for folates [44]. The issue of flour fortification with folic acid is an instructive example of protracted public health debate [45]. Although implemented in

North America, some South American countries and Australia, it is yet to be implemented in Europe. Against the certain benefits in the prevention of neural tube defects and probably other CA, particularly among women who are at high risk due to a poor diet or a lack of pregnancy planning, are the possible resistance of the public to universal additives, problems in trading flour-based products across countries with different policies and diets, and uncertainties about cancer promotion or epigenetic effects [6]. Ultimately, it is a matter of public preference how to weigh CA prevention against such uncertainties, and a consultation mechanism is needed.

The role of diet and nutrients in CA prevention is an evolving field. Interest is increasing in the effects of a low vitamin D status, which is a possible risk factor for some adverse pregnancy events, including gestational diabetes which is a recognized CA risk factor. However, the available evidence is not yet robust enough to design specific preventive actions [46, 47].

As for food contaminants, it is still difficult to assess the specific role of toxic agents in human CA, with available studies suffering from shortcomings in the measurement of actual exposure. For example, a recent case-control study found no significant association between CA and maternal dietary intake of nitrates, nitrites and nitrosamines; however, the study was limited to live births, and, mainly, the intake was estimated by a food frequency questionnaire. Moreover, no attempt was made to assess a possible combined effect of the chemicals [48]. Indeed, the problem of exposure assessment is highly relevant to environmental risk factors in general. For instance, there is ever-growing experimental evidence on the developmental effects of chemicals such as endocrine disrupters, which are suspected of increasing the risk of hypospadias [49]. The available epidemiological studies on actual environmental scenarios (e.g., water disinfection by-products, air pollution) only indicate possible correlations with CA due to limitations and inconsistencies in the study design [50], whilst growing attention toward the effects on the next generation is leading to more conservative assessments of toxicants in food and in the environment. For instance, the EFSA has recently tackled the issue of a better protection of the developing nervous system by proposing lower and more conservative reference intakes for methylmercury [51] and neonicotinoid pesticides [52]. These assessments point out a critical and emerging aspect beyond CA: the long-term sequelae of insults that do not elicit morphological disruptions but interfere with the developmental programming and/or with the organism's ability to cope with stressors in post-

natal life [53]. The risk assessments of lead [54] and methylmercury [51] in human diet based mainly on the impact of prenatal exposure on postnatal cognitive and behavioral development is an example. Another issue of the major public health impact is prenatal stress, leading to a low birth weight with an increased risk of metabolic syndromes, an unwanted consequence of a developmental adaptive response [55]. In the field of toxicology, the testicular dysgenesis syndrome is characterized by male infertility and testicular cancer in adult life as well as by an increased risk of CA of the lower urinary tract and genital tract such as hypospadias and cryptorchidism. Increasing evidence points to a relationship of exposure during testicular organogenesis to toxicants associated with lifestyle (e.g., maternal smoking) or the environment (endocrine disrupting chemicals) [56]. The impact on developmental programming opens a wide area of research on the modulation of the epigenome, the mechanism underlying developmental plasticity caused by the gene-environment interface [53]. Whereas the issue of developmental programming is still largely a research topic, it is critical to use the available scientific evidence on delayed developmental adverse (or protective) effects in order to effectively support the next generation's health [51, 54]. It is important that in all policies with potential health impact, we specifically consider the possible enhanced sensitivity and vulnerability of the fetus. Moreover, targeting only pregnant women for protection can never be more than a partial answer, since organogenesis occurs very early in pregnancy, before many women know they are pregnant.

Our general considerations and selected examples point out the need to integrate primary prevention of CA in national plans on RD and in national public health recommendations in general. The EUROCAT-EUROPLAN recommendations present an array of feasible and evidence-based measures from which national plans can

adopt and implement part of or all the actions considered by the recommendations based on individual country priorities [5]. Primary prevention of CA is feasible because many risk factors are recognized and can be targeted by well-identified community actions, such as the counselling of fertile women with chronic disease regarding medication choices, evidence-based vaccination policies and regulations on occupational exposures of either pregnant women and women of childbearing age in the workplace as well as through individual information and empowerment: taking periconceptional folic acid supplements at the right time and in the right dose, avoiding over- or underweight, and promoting alcohol avoidance in women who are pregnant or could become pregnant. The results of scientific research, identifying new risk factors and/or new aspects of recognized risk factors can develop and strengthen these actions.

Finally, primary prevention of CA is something that can be achieved here and now. Previously, cardiovascular disease and cancer were considered tragic acts of fate, but we now see them as preventable: this same change in the public health attitude is needed for CA. An integrated and coordinated primary prevention plan can identify priority targets and optimize the use of current and future resources reducing the short- and long-term health burden for the new generation.

Acknowledgements

This paper was made possible with the help of the EUROPLAN project, coordinated by the Italian National Centre for Rare Diseases (Istituto Superiore di Sanità), is included in the EUCERD Joint Action (grant No. 2011 22 01) and cofunded by the EU Commission (DG-SANCO) as well as by the EUROCAT Joint Action 2011–2013 (grant No. 2010 22 04) – a project funded by the Public Health Programme 2008–2013 of the EU Commission and coordinated by the University of Ulster, Ulster, UK.

References

- 1 World Health Organization: Congenital anomalies. Fact sheet No. 370, updated January 2014. <http://www.who.int/mediacentre/factsheets/fs370/en/#> (accessed August 28, 2014).
- 2 Whitworth M, Dowswell T: Routine pre-pregnancy health promotion for improving pregnancy outcomes. *Cochrane Database Syst Rev* 2009;CD007536.
- 3 Gilbert-Barnes E: Teratogenic causes of malformations. *Ann Clin Lab Sci* 2010;40:99–114.
- 4 WHO Guidelines on Preventing Early Pregnancy and Poor Reproductive Outcomes among Adolescents in Developing Countries. Systematic Review. Geneva, WHO, 2011.
- 5 Taruscio D, Arriola L, Baldi F, Barisic I, Bermejo-Sánchez E, Bianchi F, Calzolari E, Carbone P, Curran R, Garne E, Gatt M, Latos-Bieleńska A, Khoshnood B, Irgens L, Mantovani A, Martínez-Frías ML, Neville A, Rissmann A, Ruggeri S, Wellesley D, Dolk H: European recommendations for primary prevention of congenital anomalies: a joined effort of EUROCAT and EUROPLAN projects to facilitate inclusion of this topic in the National Rare Disease Plans. *Public Health Genomics* 2014;17:115–123.
- 6 Taruscio D, Carbone P, Granata O, Baldi F, Mantovani A: Folic acid and primary prevention of birth defects. *Biofactors* 2011;37:280–284.

- 7 Honein MA, Rasmussen SA, Reefhuis J, Romitti PA, Lammer EJ, Sun L, Correa A: Maternal smoking and environmental tobacco smoke exposure and the risk of orofacial clefts. *Epidemiology* 2007;18:226–233.
- 8 Hackshaw A, Rodeck C, Boniface S: Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. *Hum Reprod Update* 2011;17:589–604.
- 9 Ungerer M, Knezovich J, Ramsay M: In utero alcohol exposure, epigenetic changes, and their consequences. *Alcohol Res* 2013;35:37–46.
- 10 Boyd PA, Haeusler M, Barisic I, Loane M, Garne E, Dolk H: Paper 1: the EUROCAT network – organization and processes. *Birth Defects Res A Clin Mol Teratol* 2011;91(suppl 1):S2–S15.
- 11 Dolk H: EUROCAT: 25 years of European surveillance of congenital anomalies. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F355–F358.
- 12 Khoshnood B, Greenlees R, Loane M, Dolk H; EUROCAT Project Management Committee; EUROCAT Working Group: Paper 2: EUROCAT public health indicators for congenital anomalies in Europe. *Birth Defects Res A Clin Mol Teratol* 2011;91(suppl 1):S16–S22.
- 13 EU Council Recommendation of June 8, 2009 on a European action in the field of rare diseases. *Off J Eur Union* 2009;C151:7–10.
- 14 Taruscio D, Gentile AE, De Santis M, Ferrelli RM, Posada de la Paz M, Hens M, Huizer J, Fregonese L, Stefanov R, Bottarelli V, Weinman A, Le Cam Y, Gavhed D, Mincaroni P, Bushby K, Frazzica RG, Donati C, Vittozzi L, Jessop E: EUROPLAN: a project to support the development of national plans on rare diseases in Europe. *Public Health Genomics* 2013;16:278–287.
- 15 EUROCAT Working Group 2012: EUROCAT special report: congenital anomalies are a major group of mainly rare diseases. EUROCAT Central Registry, University of Ulster. <http://www.eurocat-network.eu/content/Special-Report-Major-Group-of-Mainly-Rare-Diseases.pdf> (accessed August 28, 2014).
- 16 Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges (COM(2008)679 final). http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf (accessed August 28, 2014).
- 17 Rasmussen SA, Erickson JD, Reef SE, Ross DS: Teratology: from science to birth defects prevention. *Birth Defects Res A Clin Mol Teratol* 2009;85:82–92.
- 18 Czeizel AE: Birth defects are preventable. *Int J Med Sci* 2005;2:91–92.
- 19 Irani P, Bohn C, Halasan C, Landen M, McCusker D: Community health assessment: driving the need for current, easily accessible population health data. *J Public Health Manag Pract* 2006;12:113–118.
- 20 Johnson K, Posner SF, Biermann J, Cordero JF, Atrash HK, Parker CS, Boulet S, Curtis MG; CDC/ATSDR Preconception Care Work Group; Select Panel on Preconception Care: Recommendations to improve preconception health and health care – United States. A report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. *MMWR Recomm Rep* 2006;55:1–23.
- 21 Earl R, Crowther CA, Middleton P: Interventions for hyperthyroidism pre-pregnancy and during pregnancy. *Cochrane Database Syst Rev* 2013;11:CD008633.
- 22 Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E: Interventions for clinical and sub-clinical hypothyroidism pre-pregnancy and during pregnancy. *Cochrane Database Syst Rev* 2013;5:CD007752.
- 23 Mahmud M, Mazza D: Preconception care of women with diabetes: a review of current guideline recommendations. *BMC Womens Health* 2010;10:5.
- 24 Wahabi HA, Alzeidan RA, Esmaeil SA: Pre-pregnancy care for women with pre-gestational diabetes mellitus: a systematic review and meta-analysis. *BMC Public Health* 2012;12:792.
- 25 Tieu J, Middleton P, Crowther CA: Preconception care for diabetic women for improving maternal and infant health. *Cochrane Database Syst Rev* 2010;12:CD007776.
- 26 Tieu J, Bain E, Middleton P, Crowther CA: Interconception care for women with a history of gestational diabetes for improving maternal and infant outcomes. *Cochrane Database Syst Rev* 2013;6:CD010211.
- 27 Browne ML, Rasmussen SA, Hoyt AT, Waller DK, Druschel CM, Caton AR, Canfield MA, Lin AE, Carmichael SL, Romitti PA; National Birth Defects Prevention Study: Maternal thyroid disease, thyroid medication use, and selected birth defects in the National Birth Defects Prevention Study. *Birth Defects Res A Clin Mol Teratol* 2009;85:621–628.
- 28 European Food Safety Authority: Scientific opinion on dietary reference values for iodine. *EFSA J* 2014;12:3660.
- 29 van Zuuren EJ, Albusta AY, Fedorowicz Z, Carter B, Pijl H: Selenium supplementation for Hashimoto's thyroiditis. *Cochrane Database Syst Rev* 2013;6:CD010223.
- 30 Kitzmiller JL, Wallerstein R, Correa A, Kwan S: Preconception care for women with diabetes and prevention of major congenital malformations. *Birth Defects Res A Clin Mol Teratol* 2010;88:791–803.
- 31 Shriram V, Mahadevan S, Anitharani M, Selvavinayagam, Sathiyasekaran B: National health programs in the field of endocrinology and metabolism – miles to go. *Indian J Endocrinol Metab* 2014;18:7–12.
- 32 Koloverou E, Esposito K, Giugliano D, Panagiotakos D: The effect of Mediterranean diet on the development of type 2 diabetes mellitus: a meta-analysis of 10 prospective studies and 136,846 participants. *Metabolism* 2014;63:903–911.
- 33 Popkin BM, Slining MM: New dynamics in global obesity facing low- and middle-income countries. *Obes Rev* 2013;14(suppl 2):11–20.
- 34 Karoutsou E, Polymeris A: Environmental endocrine disruptors and obesity. *Endocr Regul* 2012;46:37–46.
- 35 Opray N, Grivell RM, Deussen AR, Dodd JM: Directed preconception health programs and interventions for improving pregnancy outcomes for women who are overweight or obese (protocol). *Cochrane Database Syst Rev* 2014;1:CD010932.
- 36 Sotres-Alvarez D, Siega-Riz AM, Herring AH, Carmichael SL, Feldkamp ML, Hobbs CA, Olshan AF; National Birth Defects Prevention Study: Maternal dietary patterns are associated with risk of neural tube and congenital heart defects. *Am J Epidemiol* 2013;177:1279–1288.
- 37 Haider BA, Bhutta ZA: Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database Syst Rev* 2006;4:CD004905, update in *Cochrane Database Syst Rev* 2012;11:CD004905.
- 38 Czeizel AE, Dudás I, Vereczkey A, Bánhidy F: Folate deficiency and folic acid supplementation: the prevention of neural-tube defects and congenital heart defects. *Nutrients* 2013;5:4760–4775.
- 39 De-Regil LM, Fernández-Gaxiola AC, Dowswell T, Peña-Rosas JP: Effects and safety of periconceptional folate supplementation for preventing birth defects. *Cochrane Database Syst Rev* 2010;10:CD007950.
- 40 Obeid R, Holzgreve W, Pietrzik K: Is 5-methyltetrahydrofolate an alternative to folic acid for the prevention of neural tube defects? *J Perinat Med* 2013;41:469–483.
- 41 Denny KJ, Jeanes A, Fathe K, Finnell RH, Taylor SM, Woodruff TM: Neural tube defects, folate, and immune modulation. *Birth Defects Res A Clin Mol Teratol* 2013;97:602–609.
- 42 Guan Z, Wang J, Guo J, Wang F, Wang X, Li G, Xie Q, Han X, Niu B, Zhang T: The maternal ITPK1 gene polymorphism is associated with neural tube defects in a high-risk Chinese population. *PLoS One* 2014;9:e86145.
- 43 Bitzer J, von Stenglin A, Bannemerschult R: Women's awareness and periconceptional use of folic acid: data from a large European survey. *Int J Womens Health* 2013;5:201–213.
- 44 Stamm RA, Houghton LA: Nutrient intake values for folate during pregnancy and lactation vary widely around the world. *Nutrients* 2013;5:3920–3947.
- 45 Fajardo V, Varela-Moreiras G: Efficacy of adding folic acid to foods. *Int J Vitam Nutr Res* 2012;82:177–186.
- 46 Wei SQ: Vitamin D and pregnancy outcomes. *Curr Opin Obstet Gynecol* 2014;26:438–447.

- 47 Harvey NC, Holroyd C, Ntani G, Javaid K, Cooper P, Moon R, Cole Z, Tinati T, Godfrey K, Dennison E, Bishop NJ, Baird J, Cooper C: Vitamin D supplementation in pregnancy: a systematic review. *Health Technol Assess* 2014;18:1–190.
- 48 Huber JC Jr, Brender JD, Zheng Q, Sharkey JR, Vuong AM, Shinde MU, Griesenbeck JS, Suarez L, Langlois PH, Canfield MA, Romitti PA, Weyer PJ; National Birth Defects Prevention Study: Maternal dietary intake of nitrates, nitrites and nitrosamines and selected birth defects in offspring: a case-control study. *Nutr J* 2013;12:34.
- 49 Latini G, Knipp G, Mantovani A, Marcovecchio ML, Chiarelli F, Söder O: Endocrine disruptors and human health. *Mini Rev Med Chem* 2010;10:846–855.
- 50 Nieuwenhuijsen MJ, Dadvand P, Grellier J, Martinez D, Vrijheid M: Environmental risk factors of pregnancy outcomes: a summary of recent meta-analyses of epidemiological studies. *Environ Health* 2013;12:6.
- 51 European Food Safety Authority: Scientific opinion on the risk for public health related to the presence of mercury and methylmercury in food. *EFSA J* 2012;10:2985.
- 52 European Food Safety Authority: Scientific opinion on the developmental neurotoxicity potential of acetaminophen and imidacloprid. *EFSA J* 2013;11:3471.
- 53 Barouki R, Gluckman PD, Grandjean P, Hanson M, Heindel JJ: Developmental origins of non-communicable disease: implications for research and public health. *Environ Health* 2012;11:42.
- 54 European Food Safety Authority: Scientific opinion on lead in food. *EFSA J* 2010;8:1570.
- 55 Rinaudo P, Wang E: Fetal programming and metabolic syndrome. *Annu Rev Physiol* 2012;74:107–130.
- 56 Juul A, Almstrup K, Andersson AM, Jensen TK, Jørgensen N, Main KM, Rajpert-De Meyts E, Toppari J, Skakkebaek NE: Possible fetal determinants of male infertility. *Nat Rev Endocrinol* 2014;10:553–562.